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ORIGINAL ARTICLE

Increased arterial vascular tone during the night in patients with essential hypertension

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The time-dependent incidence of cardiovascular events points to an important role of chronobiology for arterial properties. To evaluate arterial properties in patients with essential hypertension, we assessed arterial vascular tone during sleep at night in patients with essential hypertension and normotensive control subjects. Vascular tone was continuously quantified by the reflective index obtained by non-invasive digital photoplethysmography and an algorithm for continuous, investigator-independent, automatic analysis of digital volume pulse. During the first half of the night, the reflective index was significantly higher in 31 patients with essential hypertension compared to 30 normotensive control subjects (30.0 $\pm$ 0.2 vs 28.8 $\pm$ 0.2; $P = 0.001$). In patients with essential hypertension, the reflective index significantly increased from 30.0 $\pm$ 0.2 in the first half (from 2301 to 0230) to 30.7 $\pm$ 0.2 in the second half (from 0231 to 0600) of the night ($n = 31$; $P = 0.027$). In normotensive control subjects the reflective index also significantly increased from 28.8 $\pm$ 0.2 in the first half of the night to 30.2 $\pm$ 0.2 in the second half of the night ($n = 30$; $P = 0.001$). An increase of the reflective index tone indicated systemic vasoconstriction as confirmed by cold pressure tests and a significant correlation between arterial vascular tone and sympathetic nerve activity measured by microneurography from the peroneal nerve. Photoplethysmographic determination of arterial vascular tone demonstrated a significant increase of systemic arterial vascular tone in patients with essential hypertension during the first half of the night compared to normotensive control subjects.
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Introduction

Patients with arterial hypertension are at increased risk for cardiovascular events.[1,2] The onset of cardiovascular events shows a marked circadian variation, with the peak incidence of myocardial infarction, sudden cardiac death, and stroke in the morning.[3,4] The circadian rhythm of blood pressure has been attributed to circadian rhythms in autonomic nervous and endocrine systems.[5] Circadian variations of cardiovascular events may be due in part to changes of sympathetic activity which can be associated with increased arterial vascular tone and increased risk for cardiovascular events.[6,7]

In order to assess arterial vascular tone non-invasive and easy to use techniques are desirable. The transmission of red and infrared light through the finger pulp, measured by photoplethysmography, is proportional to vascular tone and blood volume. Hence, digital volume pulse can be measured using fingertip photoplethysmography. These measurements of digital volume pulse have been described by several authors, including our group, to study vascular function in humans.[8–16] The systemic effects of vasoactive substances including glycerol trinitrate produce marked changes of the digital volume pulse.[8,9] As outlined by Chowienczyk *et al*.[9] changes of digital volume pulse can be used to quantify the systemic effects of vasoactive substances since accompanying changes of heart rate and blood pressure are minor in comparison to those of digital volume pulse. The contour of the digital volume pulse wave is determined by characteristics of the systemic circulation. As reported by Millasseau *et al*.[11] the systolic peak component arises mainly from a forward-going pressure wave. The shoulder region of the diastolic component arises mainly from pressure waves reflected back along the aorta from small arteries in the lower body. Finally, Woodman *et al*.[13] showed a strong association

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between digital volume pulse wave and markers of arterial stiffness including central (carotid-femoral) pulse wave velocity and the augmentation index obtained from applanation tonometry.

We recently reported that changes of digital volume pulse characterize impaired vascular function in renal transplant recipients.[16] Now, we used this photoplethysmographic method for non-invasive measurements of arterial vascular tone during the night without disturbing the subjects' sleep. In the present study, we tested the hypothesis whether continuous analysis of arterial vascular tone using this plethysmographic method shows differences in vascular tone in patients with essential hypertension during the night. We used an algorithm for continuous analysis of digital pulse waves, which allowed investigator-independent assessment of arterial vascular tone. Our photoplethysmographic determination of arterial vascular tone demonstrated an increase of systemic arterial vascular tone in patients with essential hypertension during the first half of the night compared to normotensive subjects.

Methods

Subjects

Thirty normotensive control subjects and 31 age-matched patients with untreated essential hypertension were enrolled in the study. Control subjects and patients with essential hypertension were prospectively recruited among subjects screened for hypertension that were free of major medical illness or other acute conditions and agreed to participate in the study. The clinical and biochemical characteristics of the subjects are shown in Table 1. After a rest of 10 min, seated blood pressure measurements were obtained. A diagnosis of hypertension was based on a blood pressure of more than 140/90 mm Hg or an isolated systolic hypertension with a systolic blood pressure of more than 140 mm Hg on more than three occasions. Patients with grade 1 (mild) and grade 2 (moderate) hypertension were studied.[17] A diagnosis of essential hypertension was established after exclusion of secondary forms of hypertension by appropriate clinical, radiological and laboratory examinations. Nineteen patients had isolated systolic hypertension and 12 patients had systolic and diastolic essential hypertension. Metabolic syndrome in patients with elevated blood pressure was diagnosed in those overweight patients (body mass index more than 25 kg/m^2) fulfilling two of the following criteria: serum triglycerides more than 1.7 mmol/l, HDL-cholesterol $<$1.04 mmol/l for men or 1.30 mmol/l for women, or fasting glucose more than 6.1 mmol/l. In patients with essential hypertension eight patients had a metabolic syndrome. Subjects did not use antihypertensive medication or sleeping pills. Subjects were studied in a quiet, temperature-controlled room. Measurements were started after a rest of at least 60 min in the supine position. Measurements during the night were performed continuously starting at 2301 and ending at 0600 without disturbing the subject. The measurements were approved by the local ethics committee and all individuals gave written informed consent.

Digital photoplethysmography

We non-invasively measured digital volume pulse using fingertip photoplethysmography. The basic

Table 1 Clinical and biochemical characteristics of 30 healthy control subjects (NT) and 31 patients with essential hypertension (HT). Continuous data are shown as mean$\pm$s.e.m.

Characteristic	*NT*	*HT*	P-*value*
Age (years)	60$\pm$3	66$\pm$2	0.099
Male (%)	57	39	0.203
Body weight (kg)	74.5$\pm$2.8	77.3$\pm$ 3.3	0.521
Body mass index (kg/m^2)	25.6$\pm$0.6	27.4$\pm$0.9	0.117
Heart rate (/min)	72$\pm$2	71$\pm$2	0.703
Systolic blood pressure (mm Hg)	125$\pm$2	158$\pm$3	0.001
Diastolic blood pressure (mm Hg)	72$\pm$2	85$\pm$2	0.001
Pulse pressure (mm Hg)	53$\pm$2	73$\pm$3	0.001
Leukocytes (/nl)	8.0$\pm$0.7	7.9$\pm$0.4	0.867
Hemoglobin (g/dl)	13.2$\pm$0.4	13.7$\pm$0.4	0.403
Platelets (/nl)	259$\pm$18	266$\pm$19	0.800
Serum creatinine (μmol/l)	81$\pm$3	86$\pm$6	0.551
Blood urea nitrogen (mmol/l)	3.2$\pm$0.4	3.8$\pm$0.9	0.588
Total protein (g/l)	69$\pm$1	68$\pm$2	0.605
Serum sodium (mmol/l)	138$\pm$1	139$\pm$1	0.359
Serum potassium (mmol/l)	4.2$\pm$0.1	4.1$\pm$0.1	0.786
Serum calcium (mmol/l)	2.32$\pm$0.03	2.38$\pm$0.03	0.085
Serum phosphate (mmol/l)	1.2$\pm$0.1	1.2$\pm$0.1	0.860
Glucose (mmol/l)	5.5$\pm$0.2	6.0$\pm$0.2	0.138
Total cholesterol (mmol/l)	5.1$\pm$0.3	5.0$\pm$0.2	0.860
Triglyceride (mmol/)	1.7$\pm$0.2	1.6$\pm$0.2	0.803

principles of digital photoplethysmography and its applications have been described by several authors including our group previously.[8–16] Digital pulse waves were measured by the transmission of red and infrared light through the finger pulp.[18] Photoplethysmography was conducted using a Vitaguard VG3000 monitor (getemed, Teltow, Germany) with the sensor (LNOP-Adt SpO2 sensor; Massimo Corporation, CA, USA) located at the third digit of the hand. Compared to other non-invasive techniques for the determination of vascular tone including applanation tonometry or ultrasound, movements of the patient or changes in pressure applied to the skin are of minor importance using digital photoplethysmography. The sensor was fixed to the third digit of the hand using an adhesive tape, not a finger clip, ensuring a comfortable adjustment of the sensor to the individual patient's finger circumference. Photoplethysmographic measurements were performed in subjects lying in supine position. Orthostatic changes were omitted during the study. Raw data were continuously collected at a rate of 32 per second and transferred to a personal computer. The first derivative of the digital pulse wave was calculated (GraphPad prism 3.0, Graph Pad Software, San Diego CA, USA). Then the local minimum of the first derivative was determined, and the corresponding first turning point (=inflection point=point of contraflexure) after the maximum in the downslope of the pulse wave was thereby exactly defined. The reflective index was calculated from the mean of the third to the seventh data point after the first turning point (=inflection point) after the maximum of the digital pulse wave. The area covered by the reflective index thereby represents the 'shoulder region' of the diastolic component of the digital volume pulse wave, which arises from pressure waves reflected back along the aorta from small arteries.[13] Each reflective index was normalized to the amplitude of the first peak of the digital volume pulse wave which was set to 100. Data of the reflective index obtained from all single digital volume pulse waves were averaged every 2.5 min. As such, the reflective index represents the mean value from 150 to 250 digital volume pulse waves obtained during a period of 2.5 min 24 data points were obtained for each single person for each hour during the night, 84 data points were obtained for each single person for one half of the night, and finally more than 2000 data points were obtained for the whole group for one half of the night.

Additional measurements were performed in healthy control subjects to characterize the reflective index during systemic vasoconstriction, increased pressure wave reflection, or vasodilation. These stress tests combined with measurements of arterial tone were performed in control subjects before the start of the measurements. Stress tests were not performed during sleep since imaging of undisturbed sleep was intended. Systemic vasoconstriction was induced by ice-cold water immersion of the contralateral hand (so-called cold pressure test). Increased pressure wave reflection back along the aorta from the lower body was induced by suprasystolic inflation of a cuff on the lower legs. Vasodilation was induced by systemic administration of glyceryl trinitrate (0.4 mg sublingual; Pohl-Boskamp, Hohenlockstedt, Germany).

Microneurography from the peroneal nerve

Invasive intraneural recording techniques were used to obtain multifiber recordings of postganglionic muscle sympathetic nerve activity (MSNA) from the peroneal nerve as described by us previously.[19] Sympathetic nerve activity by microneurography and the reflective index by photoplethysmography were simultaneously recorded under supine resting conditions and during a cold pressure test in control subjects. Simultaneous measurements were repeated at least three times for each condition.

Statistics

Data are given as mean$\pm$s.e.m. differences were analysed using *t*-test (GraphPad Prism 3.0; Graph Pad Software for Science, San Diego, USA). Data for the reflective index during the night in patients with essential hypertension and normotensive control subjects were also compared using ANOVA with Bonferroni's multiple comparison *post hoc* test. Correlations were tested using linear regression analysis. Reproducibility data are given as Bland–Altman plots that depict percentual differences between two measurements plotted against the mean of two measurements. Bland–Altman plots quantify the average discrepancy between two measurements. Two-sided *P*-values below 0.05 were considered to indicate statistical significance.

Results

Typical digital volume pulse waves and the algorithm for the determination of the reflective index are depicted in Figure 1.

As shown in Figure 2 the arterial vascular tone was continuously measured in 31 patients with essential hypertension and 30 normotensive control subjects during sleep at night. Arterial vascular tone was quantified by the reflective index obtained from digital volume pulse. More than 4000 data points could be obtained for the whole group during the night.

For the whole night the reflective index was significantly higher in patients with essential hypertension compared to normotensive control subjects (30.3 ± 0.2 vs 29.5 ± 0.16; $P=0.001$ by *t*-test). For further temporal characterization of the differences in the arterial vascular tone, we analysed the first and second half of the night separately. During the first half of the night the reflective index was

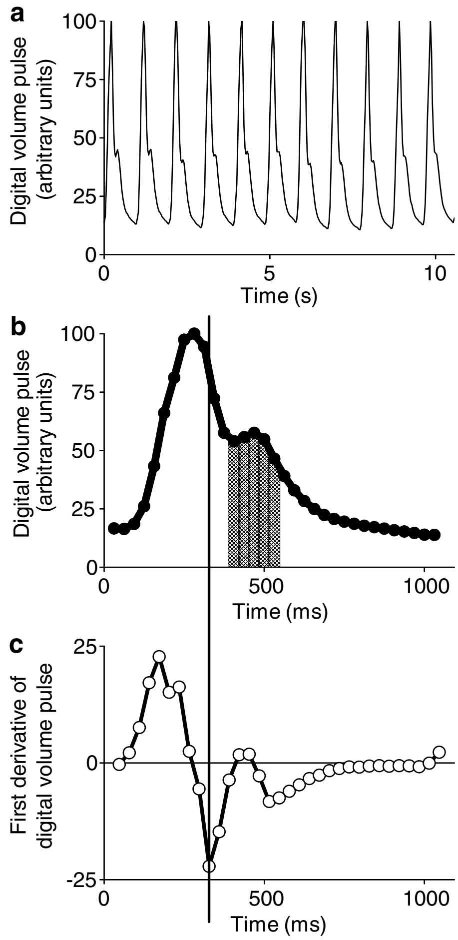

Figure 1 Assessment of the reflective index from digital volume pulse waves. (**a**) Pulse waves were measured by the transmission of red and infrared light through the finger pulp. Typical digital volume pulse waves obtained during 10 s are shown. The typical pulse wave (**b**, filled circles) and the first derivative of the pulse wave (**c**, open circles) is depicted. The local minimum of the first derivative was determined and the corresponding turning point (=inflection point) of the pulse wave was thereby defined as indicated by the vertical line. The reflective index was calculated from the mean of the third to the seventh data point after the turning point (=inflection point) as indicated by shaded area.

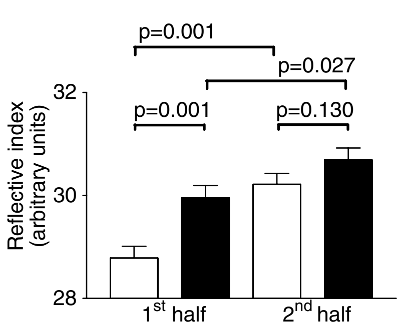

Figure 2 Arterial vascular tone during the night in 31 patients with essential hypertension (black bars) and 30 normotensive control subjects (open bars). The reflective index during the first half of the night (from 2301 to 0230) and during the second half of the night (from 0231 to 0600) was measured. Data were compared using *t*-test as indicated.

significantly higher in patients with essential hypertension compared to normotensive control subjects (30.0 ± 0.2 vs 28.8 ± 0.2; $P=0.001$ by *t*-test). In contrast, during the second half of the night the reflective index was not significantly different between patients with essential hypertension and normotensive control subjects (30.7 ± 0.2 vs 30.2 ± 0.2; $P=0.130$ by *t*-test). Also, the analysis of the data with ANOVA and Bonferroni's multiple comparison *post hoc* test confirmed that the reflective index was significantly higher in patients with essential hypertension compared to normotensive control subjects during the first half of the night ($P<0.01$), but not during the second half of the night ($P>0.05$).

In patients with essential hypertension the reflective index significantly increased from 30.0 ± 0.2 in the first half (from 2301 to 0230) to 30.7 ± 0.2 in the second half (from 0231 to 0600) of the night ($n=31$; $P=0.027$ by *t*-test). In normotensive control subjects the reflective index also significantly increased from 28.8 ± 0.2 in the first half of the night to 30.2 ± 0.2 in the second half of the night ($n=30$; $P=0.001$ by *t*-test).

The analysis of clinical parameters which might influence arterial vascular tone showed no significant correlation between the reflective index and body weight, body mass index, serum creatinine, blood urea nitrogen, serum sodium, potassium, calcium, phosphate, total cholesterol or triglycerides in either group.

To verify the reliability of reflective index measurements repeated determinations in 20 normotensive control subjects were performed (Figure 3). There was a strong correlation between the first and the second determination of the reflective index ($r^2=0.87$; $P<0.0001$). Analysing the data according to Bland–Altman confirmed a good reproducibility of measurements (bias, −4%). In addition, determinations of the reflective index on two consecutive days showed a strong correlation ($r^2=0.70$; $P<0.0001$) and a good reproducibility according to Bland–Altman (bias, 14%). Further, determinations of the reflective index were performed on both hands. There was a strong correlation between determinations of the reflective index on the right hand and the left hand ($r^2=0.86$; $P<0.0001$) and a good reproducibility according to Bland-Altman (bias, −12%).

Next, to emphasize that the reflective index is a measure of arterial vascular tone and pressure wave reflection we determined the behaviour of the reflective index during systemic vasoconstriction, increased pressure wave reflection, and vasodilation. Systemic vasoconstriction significantly increased the reflective index from 23.8 ± 2.1 to 37.4 ± 3.4 ($n=14$ subjects; $P=0.001$; Figure 4a and b) during cold pressure test. Moreover, simultaneous measurements of sympathetic nerve activity by microneurography showed a close correlation between the reflective index and sympathetic nerve

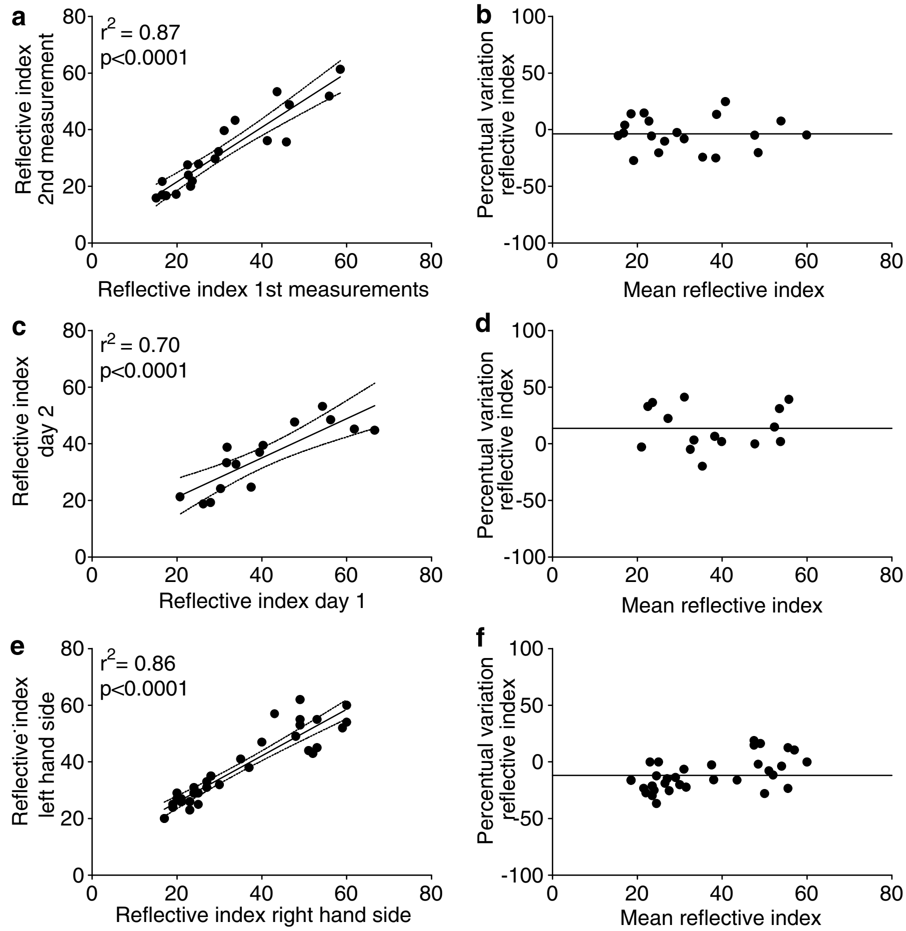

Figure 3 Reproducibility of the reflective index. The reflective index was determined in control subjects at two different time points on the same day (**a**, regression curve; **b**, Bland–Altman plot; $n = 20$), on two consecutive days (**c**, regression curve; **d**, Bland–Altman plot; $n = 15$), and simultaneously on the right hand side and the left hand side (**e**, regression curve; **f**, Bland–Altman plot; $n = 36$). Regression lines and 95% CI (dotted lines) are shown. In Bland–Altman plots, which quantify the average discrepancy between two measurements, the bias is indicated by line.

activity under supine resting conditions and during a cold pressure test (Figure 4c). An increased sympathetic nerve activity during cold pressure test was accompanied by an increased reflective index. Similarly, increasing the peripheral pulse pressure wave reflection by suprasystolic inflation of a cuff on the lower legs increased the reflective index from 32.5 ± 4.0 to 41.7 ± 4.7 ($n = 11$ subjects; $P = 0.001$; Figure 4d). On the other hand, systemic administration of the vasodilator glyceryl trinitrate significantly reduced the reflective index from 35.8 ± 4.0 to 16.1 ± 0.9 ($n = 15$ subjects; $P = 0.001$; Figure 4e).

Discussion

The present study shows an increased systemic arterial vascular tone determined by digital volume pulse measurements in patients with essential hypertension compared to normotensive control subjects at sleep.

Impairment of arterial vascular tone in patients with essential hypertension was identified by photoplethysmography of digital volume pulse as described previously.[8–16] According to recent literature photoplethysmographic measurements allow the quantitative evaluation of digital volume pulse.[9] As reported by Millasseau *et al.*,[11] the analysis of digital volume pulse provides a simple and reproducible measure of arterial vascular tone. Furthermore, Chowienczyk *et al.*[9] showed that systemic administration but not local infusion of glycerol trinitrate into brachial artery affected the photoplethysmogram waveform, indicating that systemic rather than local changes can be detected by photoplethysmography of digital volume pulse. The second derivative of the photoplethysmogram waveform has been used to characterize vascular function and Takazawa *et al.*[8] reported the effects of vasoactive drugs and aging in the photoplethysmographic waveform using this method. They showed that increased wave reflection due to vasoconstriction after systemic administration of angiotensin II or reduced wave reflection due to vasodilation after systemic administration of glycerol trinitrate mainly affected the diastolic component of the digital pulse

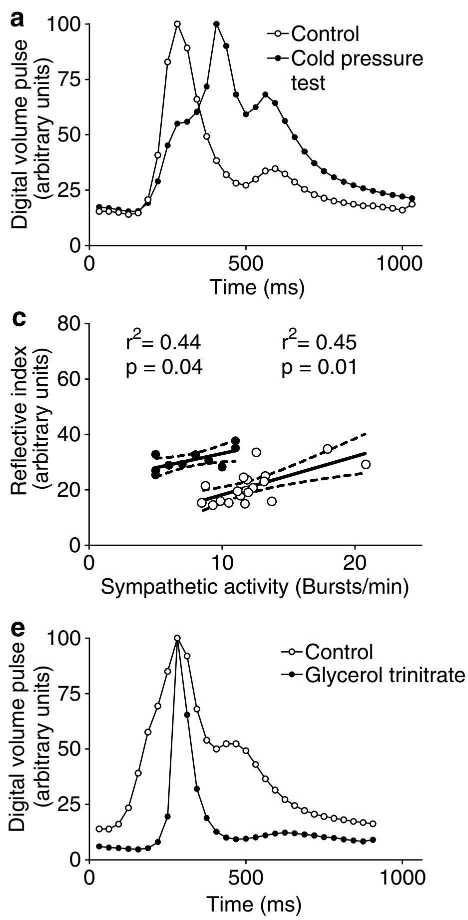

Figure 4 The reflective index as a measure of systemic arterial vascular tone. (**a**) Typical pulse wave under control conditions (open circles) and during cold pressure test (filled circles) using ice-cold water immersion of the contralateral hand. (**b**) Bar graph showing mean ± s.e.m. of the reflective index under control conditions (open bar) and during cold pressure test (filled bar; $*P=0.001$, $**P=0.001$; $n=14$ subjects). (**c**) Correlation between reflective index and sympathetic nerve activity, measured by invasive microneurography from the peroneal nerve, obtained under supine resting conditions and during a cold pressure test in two subjects (subject 1, filled circles; subject 2, open circles). Regression lines and 95% CI are shown. (**d**) Typical pulse wave under control conditions (open circles) and during increased peripheral pulse pressure wave reflection by suprasystolic inflation of a cuff on the lower legs (filled circles) (**e**) Typical pulse wave under control conditions (open circles) and after systemic administration of the vasodilator glyceryl trinitrate (filled circles).

wave. In accordance with these findings in the present study, we showed that the reduction of arterial vascular tone after systemic administration of glycerol trinitrate caused a reduction of the reflective index.[8] We demonstrated that increased arterial vascular tone due to sympathetic activation resulting in systemic vasoconstriction could be determined by changes of the digital pulse wave and quantified by an increased reflective index. We observed a linear correlation between reflective index and sympathetic nerve activity, measured by microneurography from the peroneal nerve. These data support the notion that the reflective index can be used as a marker of systemic vascular tone. Likewise, suprasystolic pressure cuff inflation around the tights is expected to increase pressure wave reflection from the legs. Indeed, the increased pressure wave reflection could be depicted by an increased reflective index. From these experiments, we conclude that changes of the reflective index reliably describe systemic changes of the arterial vascular tone.

The reflective index is calculated from the shoulder region of the diastolic component of the digital volume pulse wave, which arises from pressure waves reflected back along the aorta from small arteries. An increase of the reflective index follows an increased pulse wave reflection due to vasoconstriction. Therefore, our present data suggest that the increased reflective index in patients with essential hypertension is a marker of increased vasoconstriction in these patients.

We observed an increased arterial vascular tone in patients with essential hypertension compared to normotensive control subjects during the whole night. Furthermore, the arterial vascular tone was analysed separately for the first and second half of the night. Multiple factors which are affecting vascular tone show a circadian rhythm, for example, atrial natriuretic peptide, renin, aldosterone, or sympathetic nervous activity.[20,21] The differences of the vascular tone which we observed between the first half and the second half of the night are probably related to physiological circadian rhythms which can be observed in both normotensive control subjects and patients with essential hypertension. Other studies also have demonstrated according changes of the cardiovascular system in the second half of the night. Kario *et al.*[22] showed a slow increase of blood pressure starting during the second half of the night at about 0300 in patients with essential hypertension. Krauchi *et al.*[23] demonstrated an increasing body core temperature and heart rate in the second half of the night in healthy subjects. Furthermore, Elherik *et al.*[6] showed circadian variation of endothelial activity in normal subjects with attenuation in the morning suggesting increased arterial vascular tone in the second half of the night. These data support our observation that systemic arterial vascular tone changes during the night. However, it is interesting, that in addition our results demonstrated a significantly increased vascular tone already during the first half of the night in patients with essential hypertension. As an increased sympathetic activity has been observed in patients with essential hypertension such an increase is likely to explain the observed functional changes of arterial tone in patients with essential hypertension in the first half of the night.[21]

From a clinical point of view the significant increase of arterial vascular tone in patients with essential hypertension should be a mechanism that results in an increased central vascular tone and finally vascular disease. An arterial vascular tone which is increased over a longer time period during the night in patients with essential hypertension compared to normotensive subjects may contribute to the well-known changes of arterial structure in essential hypertension, since an increased tone results in pulse wave reflecting sides, which are closer to the ascending aorta. Such disturbances of wave reflection result in altered heart-vessel coupling and lead to increased cardiovascular risk as has been suggested by Safar *et al.*[24]

Limitations of the study

It constitutes a limitation of the present study that stress tests including the determination of vasoconstriction and increased pulse pressure wave reflection could only be performed before the start of the measurements during the night, although stress tests during the course of the night would have been insightful. However, stress tests were not performed during sleep since imaging of undisturbed sleep was intended. A further limitation of the study exists in the fact that correlations between arterial vascular tone and sympathetic nerve activity measured by microneurography from the peroneal nerve were obtained only in a few subjects. Additional measurements including atrial natriuretic peptide, renin, aldosterone and sympathetic nervous activity would be desirable to circumstantiate the present findings.

In summary, our non-invasive technique demonstrated an increase of systemic arterial vascular tone in patients with essential hypertension during the first half of the night compared to normotensive control subjects.

What is known about topic
- Patients with arterial hypertension are at increased risk for cardiovascular disease.
- Increased arterial vascular tone is observed in arterial hypertension.
- Continuous non-invasive measurement of arterial vascular tone during sleep has not been reported in patients with essential hypertension.

What this study adds
- Arterial vascular tone was continuously obtained during sleep by non-invasive digital photoplethysmography.
- Arterial vascular tone was significantly enhanced in patients with arterial hypertension during the night compared to normotensive control subjects.
- This increase of arterial vascular tone probably indicates systemic vasoconstriction over a longer time period during the night in patients with essential hypertension and finally augments cardiovascular risk.

Conflict of interest

None.

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